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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,107	04/12/2001	Christopher R. Tudan	SMAR012	4208

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BOZICEVIC, FIELD & FRANCIS LLP
200 MIDDLEFIELD RD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 03/31/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,107	TUDAN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 December 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *11,13 and 15-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10, 12, and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *1/30/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election of Group I, claims 1-16, drawn to a method of reducing the rate of hematopoietic cell multiplication comprising administering an effective amount of a CXCR4 agonist in the Paper of 25 June 2003 is acknowledged. Applicant's election of Group I, drawn to SEQ ID NO: 11 in the Paper of 25 June 2003 is acknowledged. Applicant's election of the species ff (SDF-1α), species cc (peptide spacer), and species dd (an internal cyclic amide bridge) in the Paper of 25 August 2003 is acknowledged. Applicant's election of Group Ia, drawn to a method of reducing the rate of hematopoietic cell multiplication comprising administering an effective amount of a CXCR4 peptide agonist in the Paper of 01 December 2003. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirements, the elections have been treated as an election without traverse (MPEP § 818.03(a)).

Claims 11, 13, and 15-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group or species, there being no allowable generic or linking claim. Election was made **without** traverse in the Papers of 25 June 2003 and 25 August 2003.

Claims 1-10, 12, and 14 are under consideration in the instant application as they read upon SEQ ID NO: 11 and the species of a peptide agonist comprising a peptide spacer, an agonist comprising an internal cyclic amide bridge, and SDF-1α.

Sequence Compliance

The Applicant's response to the Notice to Comply with Sequence Listing Requirements under 37 CFR §1.821 (14 March 2003) has been considered and is found persuasive. Therefore, the requirements set forth in the Notice to Comply (11 February 2003) are withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 30 January 2002 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Specification

2. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The following title is suggested: "CXCR4 AGONIST TREATMENT OF HEMATOPOIETIC PROGENITOR CELLS".

Claim Objections

3. Claims 8, 9, and 14 are objected to because of the following informalities: Claim 8 recites a non-elected group and claims 9 and 14 recite non-elected species. Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

4. Claims 1-10, 12, and 14 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-10, 12, and 14 of copending Application No. 10/086,177. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-10, 12, and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of reducing the rate of hematopoietic cell multiplication comprising administering an effective amount of a CXC chemokine receptor 4 (CXCR4) agonist to the hematopoietic cells wherein the CXCR4 agonist is a peptide having the sequence of SEQ ID NO: 11, does not reasonably provide enablement for a method of reducing the rate of hematopoietic cell multiplication comprising administering an effective amount of a CXCR4 agonist to the hematopoietic cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Specifically, the claims are directed to a method of reducing the rate of hematopoietic cell multiplication, comprising administering an effective amount of a CXCR4 agonist to the hematopoietic cells. The claims recite that the hematopoietic cells are hematipoietic stem cells

or hematopoietic progenitor cells. The claims recite that the cells are *in vivo* in a patient, that the patient has cancer, and that the patient requires autologous or allogeneic bone marrow or peripheral blood stem cell transplantation. The claims also recite that patient is treated with a cytotoxic agent. The claims recite that the CXCR4 agonist is a peptide (SEQ ID NO: 11), that the agonist comprises a peptide spacer linking the N-terminal sequence to the C-terminal sequence, and that the agonist also comprises an internal cyclic amide bridge. The claims recite that the peptide is encoded by a nucleic acid that hybridizes under stringent conditions to a portion of a nucleic acid encoding SDF-1α.

The specification teaches that the CXCR4 agonist SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-K20/E24-cyclic amide (agonist CTCE0021; pg 50) inhibits cell cycling in human erythroid and primitive granulopoietic cells and counteracts the cytotoxic action of Ara-C in white blood cell count (pg 51, Table 2; pg 52, lines 1-16). The specification also discloses that CTCE0021 and SDF-1(1-14)-$(G)_4$-SDF-1(55-67)-acid (agonist CTCE0013; pg 50) repress the proliferation of clonogenic erythroid and granulopoietic progenitors (pg 54, lines 28-31; Table 4). The specification teaches that CTCE0021 and CTCE0013 inhibit the proliferation of primitive human progenitor cells (pg 56, lines 5-24; Figure 7). The specification discloses that CTCE0021 inhibits the cytotoxic effects of Ara-C *in vivo* and sustains a higher level of leukocytes (pg 58, Example 10; Figure 10). However, the specification does not teach a method of reducing the rate of hematopoietic cell multiplication by administering all possible CXCR4 agonists to the hematopoietic cells *in vitro* or *in vivo*. Applicant's broad brush discussion of making and screening for CXCR4 agonists at pg 21 and 27-28 of the specification constitutes an invitation to experiment by trial and error. This is not adequate guidance, but is merely an invitation to

the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to determine which compounds might yield one with the desired agonistic activity. Such trial and error experimentation is considered undue.

Due to the large quantity of experimentation necessary to identify all possible CXCR4 agonists, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the breadth of the claims which fail to recite any agonist limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

7. Claims 1-7, 9-10, 12, and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of reducing the rate of hematopoietic cell multiplication, comprising administering an effective amount of a CXCR4 agonist to the hematopoietic cells. The claims recite that the hematopoietic cells are hematipoietic stem cells or hematopoietic progenitor cells. The claims recite that the cells are *in vivo* in a patient, that the patient has cancer, and that the patient requires autologous or allogeneic bone marrow or peripheral blood stem cell transplantation. The claims also recite that patient is treated with a cytotoxic agent. The claims recite that the CXCR4 agonist is a peptide (SEQ ID NO: 11), that

the agonist comprises a peptide spacer linking the N-terminal sequence to the C-terminal sequence, and that the agonist also comprises an internal cyclic amide bridge. The claims recite that the peptide is encoded by a nucleic acid that hybridizes under stringent conditions to a portion of a nucleic acid encoding SDF-1α.

As discussed above, the specification only teaches that specific CXCR4 agonists (such as CTCE0021 and CTCE0013) inhibit cell cycling in human erythroid and primitive granulopoietic cells, inhibit proliferation of clonogenic erythroid and granulopoietic progenitors, and inhibit the cytotoxic effects of Ara-C *in vivo* (pg 51-58). However, the specification does not teach all possible CXCR4 agonists. The brief description in the specification of a few examples of peptide CXCR4 agonists that could be generated is not adequate written description of an entire genus of CXCR4 agonists, encompassing nucleic acids, other peptides, antibodies, inorganic compounds, etc.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed"* (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-Cath* at page 1116).

The skilled artisan cannot envision the CXCR4 agonists of the encompassed methods, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The detectable signal or signaling pathway itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class.

Therefore, only a specific CXCR4 agonist having the sequence of SEQ ID NO: 11 or an agonist having the sequence of SEQ ID NO: 11 comprising a peptide spacer linking the N-terminal sequence to the C-terminal sequence and/or comprising an internal cyclic amide bridge, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-10, 12, and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Regarding claims 1-10, 12 and 14, the acronyms "CXCR4" and "SDF-1alpha" render the claims vague and indefinite. Abbreviations should be spelled out in all independent claims for clarity.

10. The term "susceptibility" in claim 6 is a relative term which renders the claim indefinite. The term "susceptibility" is not defined by the claim, the specification does not provide a

standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is not clear how the cells are susceptible or vulnerable to the cytotoxic agent. (Please note that this issue could be overcome by amending the claim to recite, for example, "...wherein the effective amount of the CXCR4 agonist is sufficient to reduce the cytoxic mediated destruction of cells caused by the cytotoxic agent"; see specification pg 12, lines 5-12).

11. Claim 10 is rejected as being indefinite because it is not clear if there should be another claimed limitation of the CXCR4 agonist. For example, in line 2, the claim recites "a)". However, there is no part "b)" recited in the claim.

12. Stringency is relative, and the art does not recognize a single set of conditions as stringent. The specification also does not provide an unambiguous definition for the term. In the absence of a recitation of clear hybridization conditions (e.g., "hybridizes at wash conditions consisting of **A** X SSC and **B** % SDS at **C**°C"), claim 14 fails to define the metes and bounds of the varying structures of nucleic acids recited in the claimed methods.

Conclusion

No claims are allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Tudan et al. Med Chem. 45(10):2024-2031, 2002.

Perez et al. Exp Hematol 32 : 300-307, 2004.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
25 March 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER